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A Histological Evaluation of Facial Suture Lines in Six Horses Aged 1 Day to 9 Years

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1 Summary

1.1 Summary

Craniofacial sutures are fibrous connections between flat bones in the skull, allowing a small amount of movement to absorb strain and load as long as they are patent. In the present study, we examined the histological appearance of facial sutures in horses of different ages. The internasal, nasofrontal and maxillolacrimal sutures were macroscopically identified and extracted from the skulls of six horses aged 1 day (two horses), 5 days, 2, 6 and 9 years and prepared into histological samples. The suture lines were then examined for width, form, cell density and morphology, vascularisation and morphology of the surrounding tissue and compared based on age.

Although macroscopically the sutures became difficult to identify in the 6- and 9-year-old horses, histologically they were clearly visible in all samples, indicating that the sutures were patent and consisted of connective tissue in all analysed horses. The sutures became subjectively narrower with lower cell density in older compared to young horses and there was a noticeable maturation from woven to cancellous bone surrounding the sutures. Vascular structures were present in all sutures regardless of age or location.

This study raises awareness of the histological suture conformation in neonatal and adult horses and their persistence into adulthood. A better understanding of the histological structure of facial sutures and continued patency into adulthood can aide in the interpretation of radiographs and computed tomography of the head and in improving treatment methods and outcomes for horses affected with suture exostosis. In addition, if biopsies are taken, clinicians have a basis on which to differentiate cells are related to the disease process from those normally occurring.

1.2 Zusammenfassung

Kopfsuturen sind bindegewebige Verbindungen zwischen benachbarten platten Knochen des Schädels. Während sie offen sind, erlauben sie wenig Bewegung, um Spannung und Last zu absorbieren. Diese Arbeit untersucht das histologische Aussehen der Kopfsuturen in Pferden verschiedenen Alters. Die Suturen internasalis, nasofrontalis und maxillolacrimalis wurden makroskopisch identifiziert und aus den Schädeln von Pferden im Alter von 1 Tag (zwei Pferde), 5 Tage, 2, 6 und 9 Jahren extrahiert. Davon wurden histologische Schnitte hergestellt. Die Suturen wurden anhand der Breite, Form, Zelldichte und Morphologie, Gefässversorgung sowie Morphologie des umliegenden Gewebes untersucht und anhand des Alters verglichen.

Obwohl die Suturen bei den 6- und 9-Jährigen nicht immer makroskopisch sichtbar waren, waren sie histologisch in allen Schnitten identifizierbar, was darauf hindeutet, dass die Suturen in allen Pferden offen waren und aus Bindegewebe bestanden. Bei den älteren Pferden waren sie subjektiv schmäler und zeigten, im Vergleich zu den Jüngeren, eine verminderte Zelldichte. Man beobachtete eine Reifung von Geflechtknochen zu Spongiosa. Gefässe waren in allen untersuchten Suturen vorhanden.

Diese Arbeit schärft das Bewusstsein des Zusammenbaus der histologischen Knochennaht in neugeborenen und erwachsenen Pferden und ihre Fortbestehung bis ins Erwachsensein. Ein besseres Verständnis darüber kann eine grosse Hilfe sein, um Röntgen- und CT-Bilder zu interpretieren, sowie um Behandlungen und Ergebnisse für von Suture Exostosis betroffenen Pferden zu optimieren. Zudem, wenn Biopsien entnommen werden, haben Kliniker eine Basis, um pathologische Befunde von Normalen zu unterscheiden.

2 Introduction

Craniofacial sutures are fibrous connective tissue articulations found between neighbouring flat bones in the skull (Jaslow 1990; Nickel *et al.* 2004; Rice 2008). Sutures not only function as connections between adjacent bones but are primary sites of osteogenesis in the skull (Rice 2008). Sutures do not have a cartilaginous precursor such as bone growth centres but rather function as intramembranous bone growth sites (Opperman 2000). A small amount of movement occurs as long as they remain patent – meaning the interdigitated bone is separated by connective tissue - which is important during birth (Rice 2008) as well as for load absorption during mastication, as researched using miniature swine (Rafferty and Herring 1999; Herring et al. 2001). In humans, the cranial sutures begin to close in the second to third decade of life, whereas the facial sutures remain patent and separated by fibrous connective tissue for much longer, fusing only in the seventh or eighth decade of life (Opperman 2000; Rice 2008). The reason for this difference is that the calvaria of the mammal has its most active period of growth during embryogenesis and shortly after birth, whereas the facial skeleton does not experience the majority of its rapid growth until adolescence (Rice 2008).

It is not known at what age the facial sutures close histologically in horses, but it stands to reason that this cannot happen until rapid facial growth has been completed (Jaslow 1990; Dixon 2014). The nasofrontal suture is recorded as closing (at least radiographically) in horses at 1 year of age (Butler *et al.* 2017).

Suture line exostosis in horses causes non-painful, usually bilateral swelling in the dorsal aspect of the equine head (Dixon 2014, Klein *et al.* 2014; Butler *et al.* 2017). Radiographs commonly show a proliferative periosteal (and endosteal) reaction and new bone growth around the suture lines characterised by a radiolucent defect and some degree of soft tissue swelling (Wyn-Jones 1985; Gibbs and Lane 1987). Several case studies have been published focusing on diagnosis, imaging and treatment options of suture exostosis in horses (Carslake 2009; Manso-Díaz and

Taeymans 2012; Dixon 2014; Klein *et al.* 2014; Klein *et al*. 2019). However, there is still a distinct lack of information on the histological morphology of equine facial sutures. Therefore, the aim of the present study was to examine facial sutures in horses aged 1 day to 9 years old in order to identify histological features of normal facial sutures. This information can then be used to better understand the disease process and hopefully optimise treatment options and outcomes. Moreover, the understanding of histological morphology of facial sutures could help in the interpretation of radiographs and computed tomography of the equine head. Based on the research of Rice (2008) and Rafferty and Herring (1999), we hypothesised that the sutures would contain fibrocytes/fibroblasts, interdigitation varying with age and anatomic location as well as osteoblasts in areas where new bone growth is expected, at least in the samples of the foals.

3 Materials and Methods

Samples from six horses ranging in age from 1 day to 9 years were taken from the Sutura internasalis, Sutura nasofrontalis and Sutura maxillolacrimalis (**Fig 1**). Since samples were taken only over a period of 2 months, the age groups were not equally distributed. The foals and horses were patients of the University of Zurich and the owners agreed to take post-mortem specimens. The foals and horses were euthanised for reasons unrelated to this study and did not present with any clinical indications of suture exostosis. The horses were not exsanguinated and suture samples were collected between one and 24 h after euthanasia.

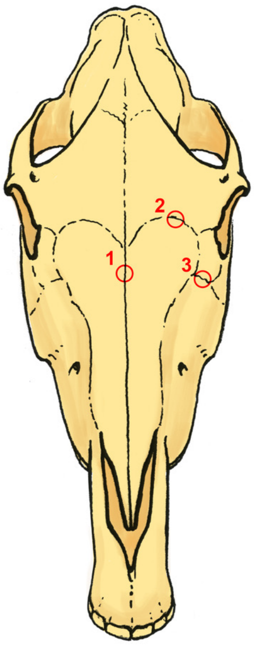

Fig 1. Equine skull showing the location of sample collection of the facial suture lines 1: Sutura internasalis. 2: Sutura nasofrontalis. 3: Sutura maxillolacrimalis.

After removal of the skin and subcutaneous tissue over the expected Sutura, the bone was exposed until the Sutura was identified. Then sections of bone of 1.5 x 1.5 cm were removed from the selected sites with a mallet and hammer, with the Sutura in the middle of the sample. Samples of all three sutures were collected for all horses except the 5-day-old foal, where only the Sutura maxillolacrimalis could be evaluated and the 6-year-old horse, where only the specimens of the internasal and nasofrontal (MMA sample only) suture could be evaluated.

The specimens were fixed in a 4% formaldehyde solution. The specimens were divided into two pieces: One part was completely decalcified with EDTA for two months and then embedded in paraffin. The second part was incompletely decalcified and then infiltrated and embedded in methylmethacrylate (MMA). The paraffin sections were regularly cut in an 90° angle to the suture, after five to 10 serial sections of 2-5 µm the specimens were adapted so that some sections could be cut parallel and within the suture line. The sections were stained with haematoxylin-eosin as a routine staining. The MMA blocks were cut with a diamond coated band saw in sections (1 mm thick), mounted on polyacrylate slides and then milled with a microtome milling machine (Leica 2600®) to sections of 300 µm, which were stained with Giemsa or Giemsa eosin.

The Giemsa staining enables a good differentiation of bone and connective tissue and cartilage in MMA-sections. The MMA-sections were cut in the same directions as the paraffin sections. From the serial sections, which showed very similar results, the qualitative best sections were evaluated independently, but unblinded for age and location of the sample by three authors (L.G., L.K., H.G.). The sections where the suture lines were clearly visible were analysed for width, form, cell density and morphology, vascularisation and morphology of surrounding tissue.

The samples were viewed by the authors under a Leica DM LB2® light microscope and digital images were obtained using a Leica DC480® camera mounted on the microscope. Measurements of the sutures were made using a magnification of x50 with light microscopy. The sutures were visually examined and then measured at three locations each that appeared to fulfill the following measurement criteria: wide, narrow and most common width. The widest and narrowest measurements were recorded as well as median of the common width. The interdigitation was evaluated subjectively based on the angle of the suture loops visible in the x50 magnification – i.e. does the suture make a full 180° turn (tight interdigitation) or only 90° (mild) or somewhere in between (moderate). This is illustrated in **Fig 2**; **Fig 2a** shows a suture with mild to moderate interdigitation – the angles at which the suture changes direction are between approximately 90° and 145°. In comparison, **Fig 2b** shows a suture with tight interdigitation; the two marked suture sections run essentially parallel to one another after a short section in which the suture changes course, corresponding to an approximately 180° turn.

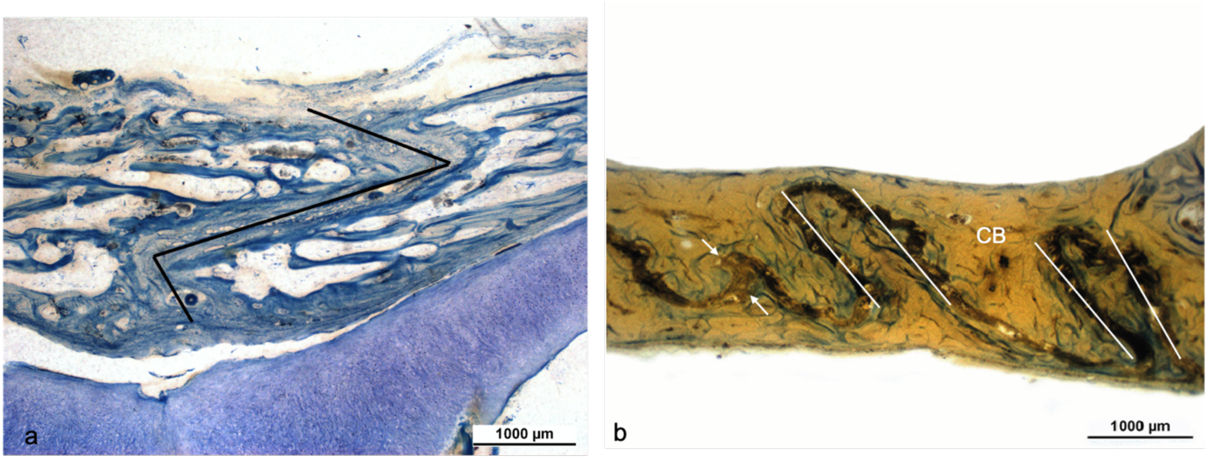

Fig 2. a: Sutura internasalis 1-day-old foal, MMA sample, Giemsa-Stain. The interdigitation is mild-moderate in this sample. b: Sutura nasofrontalis 6-year-old horse, MMA sample, Giemsa-Eosin-Stain. The suture is visible along the entire length of the sample and is denoted by an arrow. It is surrounded by mature cancellous bone (CB). The interdigitation is tight in this sample. The interdigitation was evaluated by measuring the approximate angles at which the suture changed course (lines); a directional change of 90° or less was deemed mild interdigitation, greater than 90° but less than 180° moderate and 180° tight interdigitation.

4 Results

Histologically, the sutures can be identified in the photomicrographs as structures interdigitated with surrounding bone that are composed of connective tissue (**Fig 3**). The sutures contain mostly fibrocytes and fibroblasts, but also some osteoblasts as well as blood vessels (**Fig 4**). The sutures are wider where large vessels are found within the sutures and these vessels are often concentrated in the central portion of the width of the suture. Many of the larger vessels have a diameter of approximately 200 µm. The sutures course between two adjacent skull bones, joining them together with varying levels of interdigitation (**Fig 3**).

The interdigitation of the sutures is being evaluated on a two-dimensional plane in the photomicrographs, when in reality the sutures interdigitate three-dimensionally. For this reason, the plane of intersection of the suture becomes relevant in the interpretation of the degree of interdigitation. Ideally, the photomicrographs show the suture along its length at one depth – this was approximated in several samples and is shown in **Fig 2**. However, this was not always possible to achieve macroscopically, and some samples appear to transect the suture tangentially, resulting in a non-linear view of the suture and making an evaluation of its interdigitation difficult (**Fig 5**).

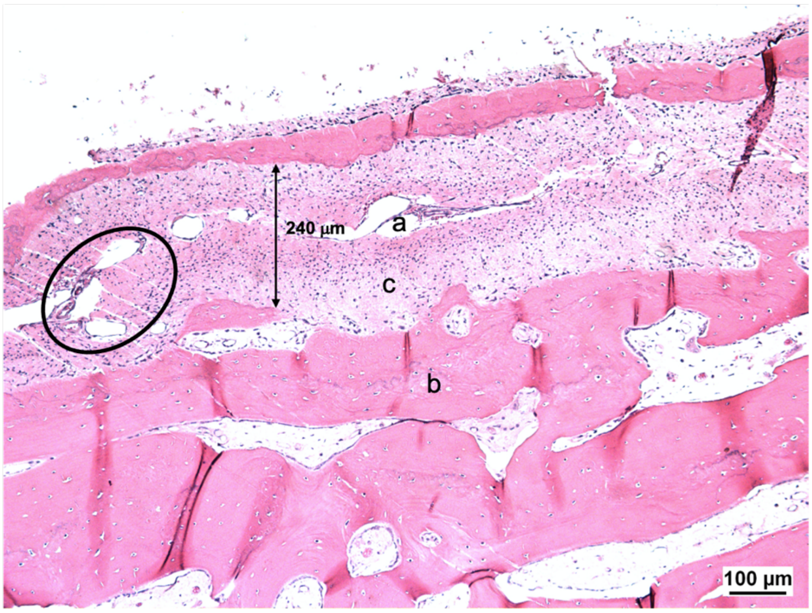

Fig. 3. Sutura maxillolacrimalis 5-day-old foal, HE Stain. Identifiable features in a suture: bundles of vessels including arterial, venous, lymphatic vessels and nerves (circled),

a: additional smaller vessels concentrated in the central portion of the width of the suture,

b: bone – in this suture woven bone with medullary cavities, c: connective tissue – in this photomicrograph the connective tissue is highly cellular. Also shown here is an example of a representative measurement of suture width (double sided arrow).

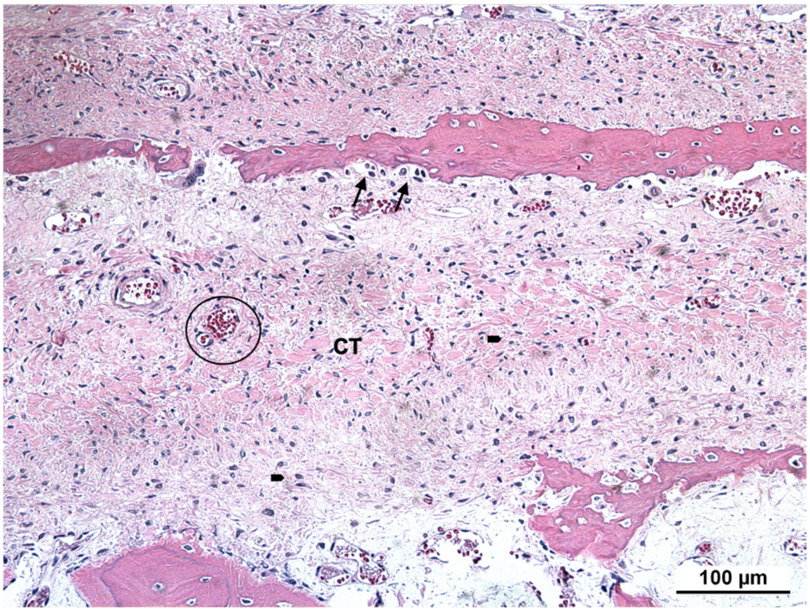

Fig. 4. Sutura maxillolacrimalis 1-day-old foal, HE Stain. The suture is composed of connective tissue (CT) with the main cells being fibrocytes and fibroblasts (arrowheads). The suture border of this foal is lined with osteoblasts (arrows). In addition, blood vessels can be seen throughout (circled).

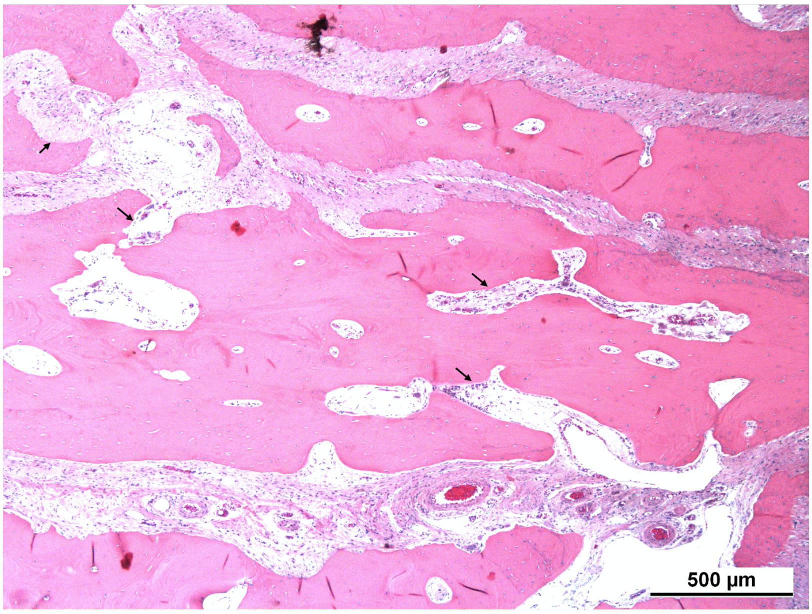

Fig. 5. Sutura maxillolacrimalis 9-year-old horse, HE Stain. It is not possible to identify a clear course of the suture and there are several projections (arrows) from the largest suture sections

that suggest the suture has been transected on more than one plane, making the interdigitation difficult to impossible to identify using this sample.

Table 1 summarises the results of representative photomicrographs in each of the age categories and sutures.

Table 1: Summary of the results
d = day, y = years

Suture	Age	Cell density	Cell types	Vascularization	Interdigitation	Median Width / µm	Widest Point / µm	Narrowest Point / µm
Internasalis	1d	high	Fibrocytes Fibroblasts some Osteoblasts	high	moderate	260	480	60
Internasalis	1d	high	Fibrocytes Fibroblasts some Osteoblasts	high	moderate	500	700	420
Internasalis	2y	moderate - high	Fibrocytes Fibroblasts some Osteoblasts	high	moderate	560	940	340
Internasalis	6y	moderate	predominantly Fibrocytes & Fibroblasts	moderate-high	moderate	320	800	160
Internasalis	9y	moderate	predominantly Fibrocytes & Fibroblasts	moderate-high	tight	200	500	80
Nasofrontalis	1d	high	Fibrocytes Fibroblasts some Osteoblasts	high	moderate-tight	200	500	100
Nasofrontalis	2y	moderate - high	Fibrocytes Fibroblasts some Osteoblasts	high	tight	200	400	50
Nasofrontalis (MMA)	6y	unable to evaluate	unable to evaluate	moderate-high	tight	200	240	100
Nasofrontalis	9y	moderate	predominantly Fibrocytes & Fibroblasts	moderate-high	tight	140	560	60
Maxillolacrimalis	1d	high	Fibrocytes Fibroblasts some Osteoblasts	high	unable to evaluate	280	1300	80
Maxillolacrimalis	2y	moderate - high	predominantly Fibrocytes & Fibroblasts	high	tight	100	400	40
Maxillolacrimalis	9y	moderate	predominantly Fibrocytes & Fibroblasts	moderate-high	tight	160	360	60
Maxillolacrimalis (MMA)	9y	unable to evaluate	unable to evaluate	moderate	moderate-tight	200	500	100

There are several features that can be used to mark the maturation of the suture as the age of the horse increases. The connective tissue is loose in the 1-day-old and 5-day-old foals and appears denser with a lower cellularity in the adult horses (**Fig 6**). Osteoblasts, which are indicators of new bone formation, are present in a higher concentration in the 1-day-old and 5-

day-old foals and rarely found in the adult horses (**Fig 7**). The borders of the suture are identified by the intersection of fibrous connective tissue with bone. In the foals and 2-year-old horse these borders have a high cellularity and walls of osteoblasts and/or fibrocytes and fibroblasts are present on the suture side of the border. In adult horses the borders are composed of connective tissue interspersed with fibrocytes (**Fig 7**). The bony interface is identified in the foals and 2-year-old horse by woven bone and medullary cavities; in the 6- and 9-year-old horses this is replaced by cancellous bone with osteons (**Figs 2b, 6** and **8**).

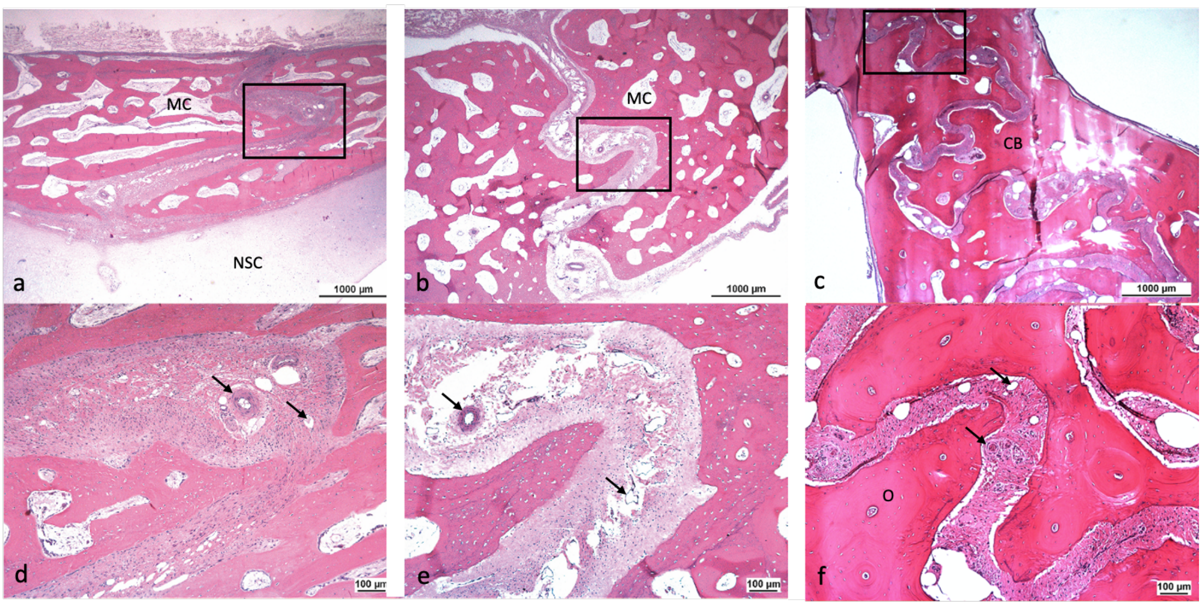

Fig 6. Sutura internasalis, HE Stain. a,d) 1-day-old foal (b,e) 2-year-old horse (c,f) 9-year-old horse. a,b,c) 25x magnification, (d,e,f) 100x magnification of the region of interest shown in the low magnification photomicrograph. Woven bone with medullary cavities (MC) can be seen on either side of the suture in both the 1-day-old and 2-year-old samples. The higher magnification reveals a highly cellular connective tissue inside the suture as well as numerous blood vessels (arrows). At the bottom of (a) the nasal septal cartilage (NSC) is prominent. The sample from the 9-year-old horse reveals cancellous bone (CB) with osteons (O) visible in the higher magnification. The connective tissue is dense and blood vessels are identifiable (arrows).

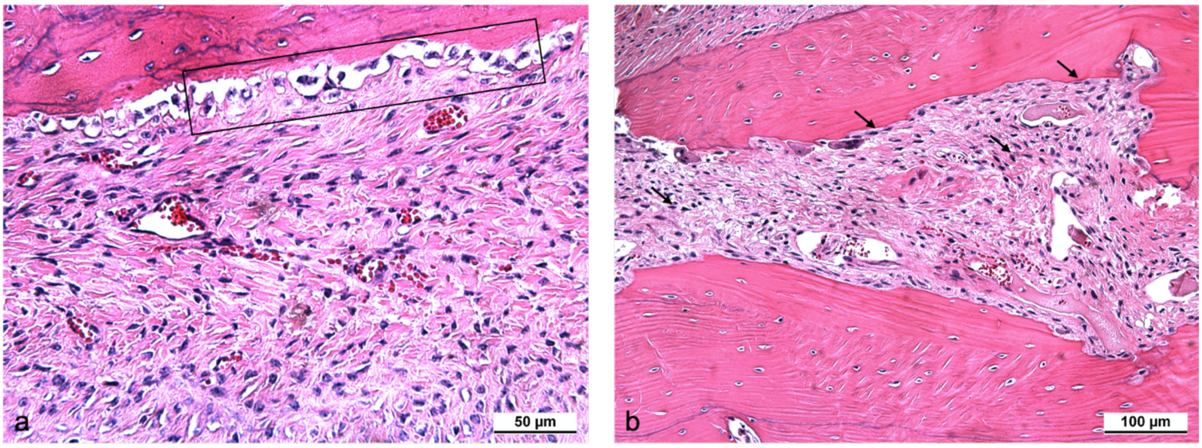

Fig 7. a) Sutura maxillolacrimalis 1-day-old foal, HE Stain. Note the row of walled in osteoblasts along the outer border of the suture (box). The high density of fibrocytes and fibroblasts can be seen in the suture along with blood vessels. b) Sutura nasofrontalis 9-year-old horse, HE Stain. The border of the suture is lined by fibrocytes (arrows), which can also be found in the connective tissue of the suture along with blood vessels.

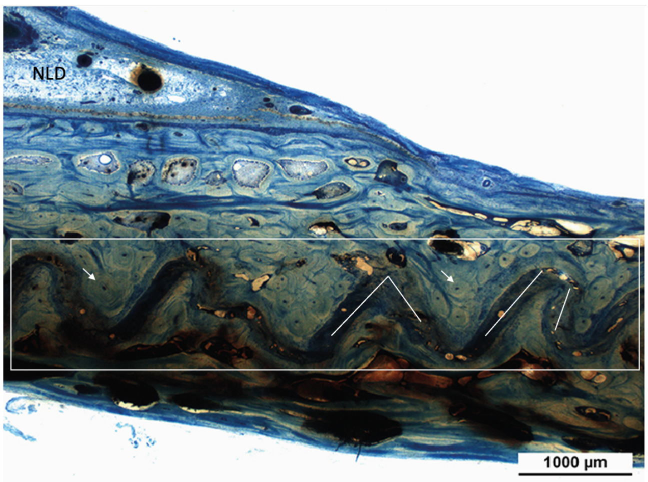

Fig 8. Sutura maxillolacrimalis, 9-year-old horse, MMA sample, Giemsa-Stain. Note the suture with its interdigitation in dark blue (box) surrounded by osteons (arrows). The interdigitation is illustrated by white lines within the suture and has been classified as moderate to tight as the directional changes of the suture are greater than 90° in the visible sample. The nasolacrimal duct (NLD) can be seen in the upper left-hand quadrant.

5. Discussion

The aim of the present study was to histologically examine the internasal, nasofrontal and maxillolacrimal sutures in horses aged 1 day to 9 years old and identify key histological features of facial sutures in horses of different ages. The sutures became increasingly difficult to identify macroscopically on the skull - the Sutura maxillolacrimalis was not identifiable in the 6-year-old horse – however, all of the sutures examined were clearly visible on histology and contained connective tissue and blood vessels. There is limited information as to proposed ages of fusion in facial sutures in horses; Butler *et al.* (2017) suggest that the nasofrontal suture is obliterated at 1 year of age, the left and right nasal bones (the internasal suture) do not fuse, and the maxillolacrimal suture is not specifically discussed, although the premaxilla suture is listed as being obliterated in the fourth year of life. However, as the authors are unaware of any previous studies examining facial suture patency in horses, these fusion times could be based on radiographic and gross visibility. The results of this study suggest that the patency of the facial sutures could be much longer than was previously thought and in fact, similar to that of the facial sutures in humans, which do not fuse until the seventh or eighth decade of life (Opperman 2000; Rice 2008).

As the horse's age increased, a progressive maturation of all three sutures was observed. This is evident through a juxtaposition of the internasal sutures of the 1-day-old foal and the 2- and 9-year-old horses, which clearly shows the change in density of the connective tissue and cellularity as well as the maturation of the adjacent bone from woven to cancellous. In fact, newborn foals have wide sutures with a high degree of highly cellular loose connective tissue and a high level of vascularisation, surrounded by woven bone. As the horse matures there is a clear reduction in the number of cells present in the suture and osteoblasts become rare.

Interpretation of width measurements in this study is prone to error because of the limited number of values obtained in each location and the width appeared to be influenced by the plane of sample transection, which appeared in some samples inconsistent. Despite this we feel that in the samples examined from individual horses there was subjectively, a slight narrowing of overall suture width from all locations with increasing horse age. This could be made more objective by using larger sample numbers, ensuring that all samples were extracted from the same anatomical location (i.e. relative location to gross landmarks irrespective of gross identification of the suture) and taking more measurements. Additionally, analysing sutures along a larger portion of their length, as well as at comparable levels of depth would provide additional information as to whether sutures tighten at similar or different rates depending on their location within/along the suture.

In all three suture locations (internasalis, nasofrontalis, maxillolacrimalis) there was clear interdigitation visible and the interdigitation seemed to increase with the age of the horse. Moreover, the serpent-like suture lines appear in all sutures not only in the outer, more horizontal plane but also in the vertical plane that connects the adjacent bones with one suture, the Sutura maxillolacrimalis in the 2-year-old horse, even appearing to be transected tangentially. However, the interpretation of the interdigitation is biased to the angle that the tissue was sectioned and therefore limited in its value. For this reason, the authors did not take a quantitative approach to describing the interdigitation of the sutures.

Mature sutures unite bone surfaces through various degrees of overlapping or interdigitation corresponding to the strain applied to it and are characterised by fibrous tissue that absorbs the load at a much higher level than the rigid skull bones are able to do (Jaslow 1990; Herring et al. 2001; Herring 2008). Research has shown that higher strain energy, and therefore a higher degree of interdigitation, in the suture corresponded to a greater ability to absorb shock (Jaslow 1990; Maloul *et al.* 2014). Three types of strain have been identified to influence the mechanical properties of sutures: impact loading, for example from falling or contact with a foreign object or intentional forces such as fighting; cyclic loading, for example during mastication; and quasi-static strain from the presence of adjacent tissues such as changes in intracranial pressure or direct strain to the facial sutures through growth of adjacent structures (Herring 2008; Moazen *et al.* 2016). Studies examining the skulls of mice and children reported an increase in suture interdigitation after birth as well as new bone growth, a dense network of collagen fibres and a high level of vascularisation in the suture borders (Rice 2008; Khonsari *et al.* 2012). Similarly, in the present study we could observe an increase of suture interdigitation between birth and adult age, suggesting an increased adaptation for shock absorption. However, what level of strain different suture lines in horses undergo during mastication is not known. In miniature swine, during normal mastication, the frontonasal suture has been shown to experience predominant compressive loading and exhibited a greater degree of interdigitation (Rafferty and Herring 1999). It can be hypothesised that in horses the frontonasal suture will also absorb the most compressive forces during mastication, which could explain why suture exostosis occurs most frequently at this location. However, we were not able to objectively identify different grades of interdigitation for each location in the present study.

This study has a number of limitations including a small sample size that does not include weanlings, yearlings or horses over the age of 9. In addition, the lack of samples where the sutures were grossly fused does not allow conclusions to be made as to how gross fusion corresponds to histological fusion. This could be improved in further research by optimising consistency of sample location among horses as well as removing a larger area of suture line for comparison. In hindsight, it would have been beneficial to evaluate gross appearance before removing bone sections from the anatomical site where the suture was expected to be located. This would also have allowed bone to be removed for analysis in horses that no longer had grossly visible sutures. However, Klein *et al.* (2019) showed that the sutures are not always located in the same anatomical location – therefore, it would be necessary to take bone samples over a much larger area in cases where the suture is not grossly visible and examine a much larger number of histological samples.

A number of methods have been suggested to evaluate suture patency, including a qualitative method first suggested by Broca in 1875 that uses a scale of 0-4 based on the macroscopically visible degree of synostosis or a more quantitative analysis of suture closure such as that used by Hershkovitz *et al.,* which measures the percentage of visible suture obliteration in order to classify a suture as totally closed, partially closed, partially open, totally open or prematurely closed (Broca 1875; Hershkovitz *et al.* 1997). Recent advancements in technology have allowed more sophisticated quantitative methods of evaluating suture morphology and patency such as 3D micro-computed tomography (μCT) (Maloul *et al.* 2010; Moazen *et al.* 2016).

In conclusion, this study demonstrates that the examined internasal, nasofrontal and maxillolacrimal sutures in horses up to 9 years of age are comprised of connective tissue and therefore histologically patent. Further studies would need to be done with horses of various ages, possibly horses up to 30 years of age, in order to determine if these results are consistent among a larger sample group and at what age the facial sutures in horses fuse.

5 Authors' declaration of interests

No conflicts of interest have been declared.

6 Ethical animal research

Not applicable.

7 Acknowledgements

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